

*EFFECTS OF Δ^9 -THC ON MARIJUANA SMOKING, DOSE CHOICE,
AND VERBAL REPORT OF DRUG LIKING*

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The effects of Δ^9 -tetrahydrocannabinol content of marijuana on cigarette smoking, dose choice, and verbal report of drug "liking" by adult males living in a residential laboratory were investigated. Marijuana cigarettes were available during programmed intervals while subjects were engaged in recreational activities. The tetrahydrocannabinol content of the cigarettes remained constant each day, but was changed across days. Subjects provided written ratings of drug liking at the end of each day. In the first study, placebo or active (2.3% Δ^9 -tetrahydrocannabinol) marijuana cigarettes were available for 1-, 2-, or 3-day intervals at varying times of day. The number of cigarettes smoked was unrelated to tetrahydrocannabinol content, although verbal reports of drug liking were consistently higher when marijuana cigarettes containing tetrahydrocannabinol were smoked. In a second study, a choice procedure, consisting of four 3-day blocks of 2 sample days and 1 choice day, was used. On sampling days, subjects smoked cigarettes varying in tetrahydrocannabinol content (0.0, 2.0, and 3.5%, w/w); on choice days they were allowed to choose between the two previously sampled doses. The number of cigarettes was not consistently related to tetrahydrocannabinol content. Ratings of drug liking were increased when marijuana cigarettes contained tetrahydrocannabinol, but ratings of marijuana containing 2.0% and 3.5% of the compound were similar. In contrast, subjects consistently chose the 3.5% dose over either the 0.0% or 2.0% dose. Dose choice was more sensitive to tetrahydrocannabinol content than either reports of drug liking or numbers of cigarettes smoked.

Key words: marijuana, Δ^9 -tetrahydrocannabinol, reinforcement, dose choice, self-administration, subjective drug effects, humans

Despite recent changes in drug use, marijuana continues to be the most commonly used illicit substance in the United States (National Institute on Drug Abuse, 1991). Marijuana is the third most commonly reported psychotropic substance used by teenagers, and has been described as an antecedent to other illicit drug use (e.g., Kandel, 1991). Despite the pur-

ported prevalence and negative consequences of marijuana smoking (e.g., Block, Farnham, Braverman, Noyes, & Ghoneim, 1990; Maykut, 1985), surprisingly little is known about the factors that maintain its use.

Drugs that are used extensively by humans are also typically self-administered by nonhuman subjects under controlled laboratory conditions (Griffiths, Bigelow, & Henningfield, 1980; Johanson & Balster, 1978). However, few studies of marijuana self-administration in nonhuman research subjects have been reported. The reasons for the limited number of studies are unclear; it may be that the reinforcing effects of marijuana are insufficient to offset aversive effects of marijuana smoke in nonhumans, that the smoking technology for nonhumans is difficult to engineer, or that factors in addition to those associated with marijuana smoke (e.g., instructions, social context, conditioning history) are critical to the initiation and perhaps maintenance of marijuana self-administration in humans.

Humans with histories of marijuana use readily self-administer marijuana in laboratory settings (e.g., Chait, 1989; Foltin, Fischman, Brady, Capriotti, & Emurian, 1989; Mello & Mendelson, 1985; Mendelson, Kuehnle, Greenberg, & Mello, 1976; Miles et

The Programmed Environment Research Center demonstrates clearly the scope of Joe Brady's impressive creativity. It was a logical yet extraordinary methodological advance, bridging the gap from the study of nonhuman behavior to the immensely difficult task of studying human behavior under relatively naturalistic conditions. Dr. Brady had the scientific vision to realize the full potential of such a behavioral laboratory, and expended an enormous effort developing and funding it. Although the laboratory was initially conceived of, in the early 1970s, in conjunction with an expanding NASA spacelab program, it could be used effectively to implement a broad range of research questions. Dr. Brady was mentor and colleague to us, generously supporting our research with enthusiasm, hard work, and unflagging optimism. We are grateful to him for all of this, and pleased to honor his many contributions.

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al., 1974; Zacny & de Wit, 1991). Although previous research has clearly identified Δ^9 -tetrahydrocannabinol (THC) as the principal pharmacological agent associated with behavioral impairment following inhalation of marijuana smoke (e.g., Foltin, Fischman, Pippen, & Kelly, 1993; Heishman, Stitzer, & Yingling, 1989; Kelly, Foltin, & Fischman, 1993), little evidence exists for a role of THC content in marijuana self-administration (cf., Chait & Zacny, 1992; Mendelson & Mello, 1984). Marijuana self-administration studies have either not examined THC content (e.g., Chait & Perry, 1992; Foltin *et al.*, 1989; Mello & Mendelson, 1985; Mendelson *et al.*, 1976) or have found no effect of THC content on smoking rates (e.g., Chait, 1989; Zacny & de Wit, 1991). Recent investigations indicate that multiple indices of the reinforcing effects of a drug are necessary for a complete assessment of abuse liability (e.g., Chait & Zacny, 1992; Foltin & Fischman, 1992). The purpose of the present studies was to examine the reinforcing effects of THC using the number of marijuana cigarettes smoked, dose choice, and verbal report of drug "liking."

EXPERIMENT 1

METHOD

Subjects

Two groups of 3 healthy adult male research volunteers, between 27 and 34 years of age (30.5 ± 1.4 years [mean \pm SEM]), who reported between 4 and 30 occasions of marijuana use per month (19.7 ± 5.3), gave written consent to participate in a 12-day study after receiving medical and psychological examinations. Reports of marijuana use were validated through urinalysis prior to the study. Subjects received per diem performance and bonus payments totaling \$550 to \$600. The protocol was approved by The Johns Hopkins University Joint Committee on Clinical Investigation.

Laboratory

The study was completed in a residential laboratory designed for continuous observation and analysis of human behavior (Brady, Bigelow, Emurian, & Williams, 1974). The laboratory consisted of six rooms interconnected by a single hallway. Three identical color-coded rooms, each equipped with a food preparation

area, a bathroom, a bed, and a task performance station, functioned as private apartments, with each subject assigned to a specific room and color. Access to the remaining three rooms, including a recreation room containing a food preparation area, lounge furniture, a videogame system, board games, and a television used for displaying videotaped movies; an exercise room equipped with exercise and laundry facilities; and a bathroom was available to all 3 subjects at programmed times. One illuminating button, labeled "MARIJUANA," was mounted on a wall in each private room, and three illuminating buttons, one for each subject, were mounted on a wall of the recreation room.

Output from video, audio, and mechanical equipment located throughout the residential facility terminated in an adjacent control room. Subjects were continuously monitored except while in private dressing and bathroom areas. Communications between subjects and staff occurred via a networked computer system. Computers were located in each private room and in the recreation room, as well as in the control room. To limit the potential effects of external events on behavior, telephones, television, newspapers, and mail were not available.

Standard Day

Subjects were awakened at 9:00 a.m. A daily 6.5-hr recreation period, during which subjects could engage in recreational activities in their private rooms (e.g., reading, listening to music) or in the social area (e.g., watching videotaped movies, playing board games) occurred once per day. For Subjects S1, S2, and S3, the 6.5-hr recreation period started at 4:30 p.m. on Days 1 through 7 and at 10:00 a.m. on Days 8 through 12. For Subjects S4, S5, and S6, the recreation period began at 10:00 a.m. on Days 1 through 7 and at 4:30 p.m. on Days 8 through 12. During other times, subjects were required to remain in their private rooms engaging in a variety of computerized performance tasks for which they received financial compensation (Kelly *et al.*, 1993). Except on Day 1, every evening between 11:00 p.m. and midnight, subjects completed visual-analogue ratings of drug "liking" by placing a mark along a 100-mm line anchored with endpoints of "dislike" on the left and "like" on the right. Ratings were scored by measuring the distance between

the left endpoint and the subject's mark. Overhead lights were turned off after subjects completed the drug-rating forms, and subjects were required to sleep or rest in their private rooms until 9:00 a.m. the next morning. Clocks and watches were not permitted, and subjects were notified via the communication system of transition times (e.g., 9:00 a.m., 4:30 p.m., etc.).

Marijuana Self-Administration

Subjects were told prior to the study that they could smoke up to eight marijuana cigarettes per day during two daily drug-availability intervals between 10:00 a.m. and 3:30 p.m. and between 4:30 p.m. and 10:00 p.m., but that cigarettes could not be smoked "back to back." A 20-min inter-cigarette interval was in effect during the availability intervals, but subjects were not informed of this duration. Subjects were also told that different strengths of marijuana would be available from day to day, but that the strength would not change during any given day.

Marijuana cigarettes were obtained by responding on the appropriately color-coded "MARIJUANA" buttons located in the private rooms or in the recreation room under a fixed-ratio (FR) 10 schedule of reinforcement. Buttons were illuminated if a marijuana cigarette was available, but remained dark if a cigarette was not available (i.e., before 10:00 a.m., between 3:30 and 4:30 p.m., after 10:00 p.m., or within 20 min of the previous marijuana cigarette). Except on Day 1, which served as a nonsmoking control day, machine-rolled unfiltered marijuana cigarettes (provided by the National Institute on Drug Abuse) containing 0% or 2.3% Δ^9 -THC (w/w) were available. Placebo cigarettes (0.0%) were available on Days 2, 3, 7, 8, and 12, with active cigarettes available on Days 4 through 6 and 9 through 11. Marijuana cigarettes were delivered with one end placed in a cigarette holder, and the other end was pinched and rolled to hide the plant material. Subjects took three puffs on a cigarette, one per minute. Each puff was cued by signal lights and consisted of a 5-s inhalation interval, a 10-s interval in which smoke was held in the lungs, and a 45-s exhalation and rest interval.

RESULTS

The left panel of Figure 1 presents the number of cigarettes smoked per day during the

recreational period. Stable patterns of marijuana smoking were observed across days in Subjects S1, S2, S3, S4, and S5, indicating that smoking during the recreation period was independent of time of day. Subjects smoked about the same number of placebo (open symbols) and active (filled symbols) cigarettes. Smoking decreased after Day 7 for S6 regardless of the THC content of the marijuana cigarettes. Individual differences in smoking were also observed, with subjects smoking an average of between 1.4 (S6) and 3.4 (S5) cigarettes per recreation period.

The right panel of Figure 1 presents daily visual-analogue ratings of drug "liking." In contrast to the absence of an effect of THC content on the number of cigarettes smoked, subjects consistently reported greater "liking" scores for active compared to placebo cigarettes. The range of daily placebo marijuana "liking" ratings was lower than the range of daily active marijuana ratings for all subjects, except S1. Mean placebo ratings varied between 12.4 ± 4.4 mm by S2 to 64.0 ± 7.2 mm by S3; mean active ratings varied between 58.5 ± 3.2 mm by S4 to 88.5 ± 3.0 mm by S3.

EXPERIMENT 2

METHOD

Subjects

Two groups of 3 men between 23 and 33 years of age (28.3 ± 1.5 years), who reported between 8 and 32 occasions of marijuana use per month (22.0 ± 4.6), participated in a 14-day study. Reports of marijuana use were validated through urinalysis prior to the study. Subjects received \$15 per diem, approximately \$10 per day in task earnings, and \$420 for successfully completing the study.

Laboratory

The study was completed in the same residential laboratory, with minor modifications. Four colored illuminating buttons, labeled "red," "blue," "green," and "white," were mounted on a wall in each private room, and six additional buttons were mounted in a two-row by three-column pattern on a wall of the recreation room. Buttons in separate columns were labeled "Subject 1," "Subject 2," or "Subject 3." Lens colors and labels (i.e., "red," "blue," "green," and "white") were adjusted

Marijuana Self-Administration

VAS Liking

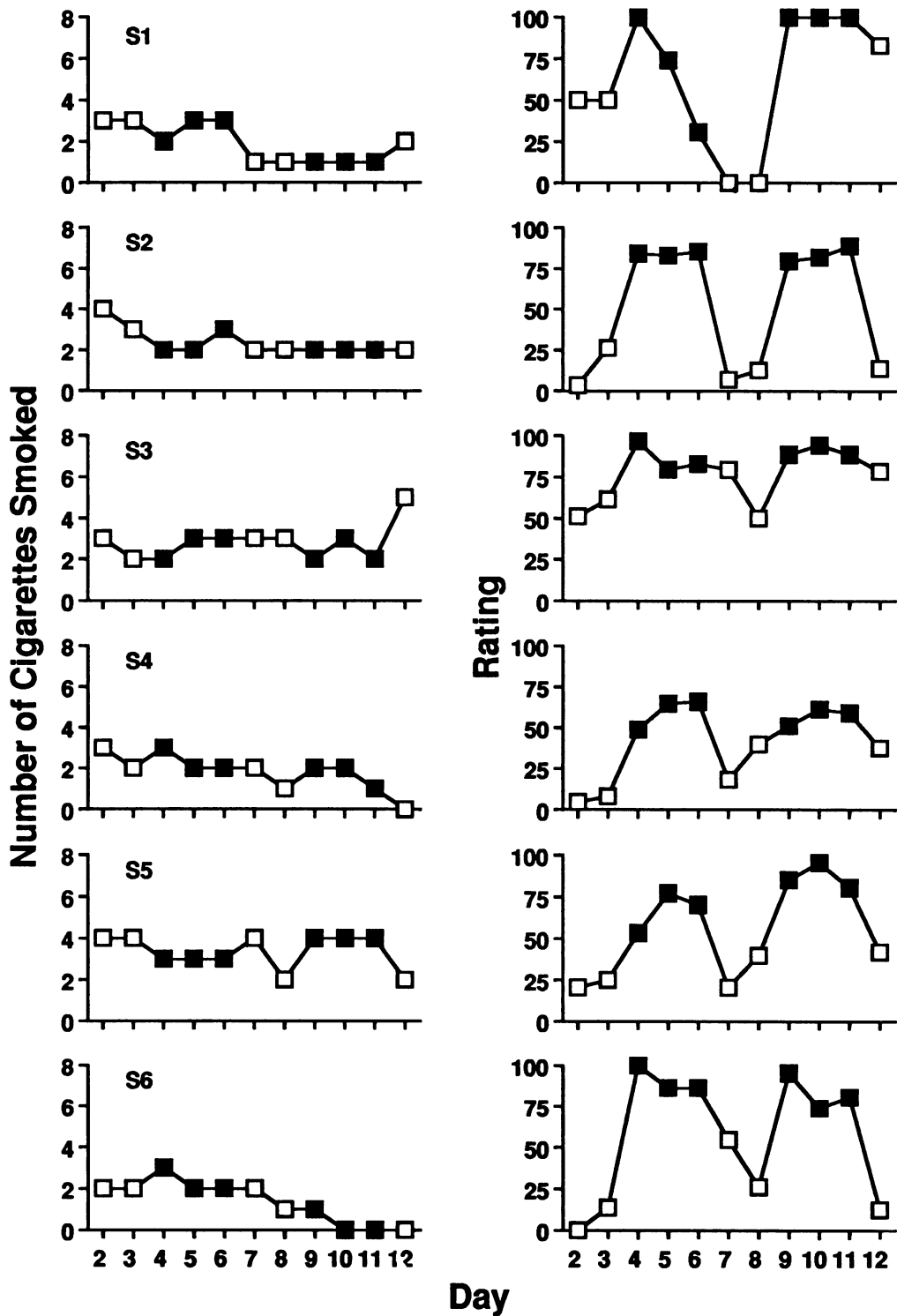


Fig. 1. Number of marijuana cigarettes smoked per day during the recreation period (left column) and visual-analogue ratings of drug “liking” (right column) for each subject. Symbol backgrounds represent dose conditions (open symbols: 0% THC; solid symbols: 2.3% THC).

during the study to match available drug conditions.

Standard Day

The daily schedule was similar to that used in the previous study; however, the 6.5-hr recreation period began every day at 5:00 p.m., with marijuana cigarettes available during the first 5.5 hr. Subjects completed daily ratings of drug "liking" at 11:30 p.m., except on Days 1 and 14.

Marijuana Self-Administration

As in the previous study, subjects could again smoke up to eight marijuana cigarettes per day, with a minimum 20-min inter-cigarette interval. Subjects were required to sample a minimum of one cigarette between 5:00 p.m. and 8:00 p.m. Prior to the study, subjects were told that the marijuana strengths available at any given time would be indicated by the illumination of colored buttons labeled "red," "blue," "green," and "white," and that the association between marijuana strength and color would not change during the study.

Color-strength pairings were the same for each member of a group but differed between the two groups. Subjects were informed that on some days, only a single color (i.e., a single marijuana strength) would be illuminated (i.e., sampling days); on other days, two colors (i.e., two marijuana strengths) would be illuminated and that the subjects would be required to choose between them (i.e., choice days).

On sampling days, the colored button in the private and recreation rooms associated with the strength of marijuana available on that day was illuminated. Cigarettes were obtained by responding on illuminated buttons under an FR 10 schedule of reinforcement. Button lights were turned off after the 10th response to signal that marijuana cigarettes would be delivered, and remained off during the 20-min inter-cigarette interval. Cigarettes were smoked according to the same puffing procedure used in the previous study.

On choice days, the colored buttons in the private and recreation rooms associated with the strengths of marijuana sampled on the two previous days were illuminated. The initial choice determined what type of cigarette would be available that day. Following the first choice, after the 20-min inter-cigarette interval had elapsed, only the chosen button was reilluminated.

Four 3-day blocks, each consisting of 2 consecutive sample days followed by a choice day during which subjects chose between doses sampled on the previous 2 days, were presented. THC strengths of 0.0% and 3.5% were sampled during the first two blocks, and strengths of 2.0% and 3.5% were sampled during the second two blocks, with order of exposure to doses on sampling days counterbalanced between groups.

RESULTS

The left panel of Figure 2 presents the number of marijuana cigarettes smoked during the recreation period each day. During the first block, with two exceptions (S2 and S3 smoked greater numbers of 3.5% THC than 0.0% THC cigarettes), the numbers of cigarettes smoked was not consistently related to THC content. During the second block, on Days 5 through 7, all 6 subjects consistently smoked more 3.5% THC cigarettes than 0.0% THC cigarettes. On the choice day of the first two blocks (i.e., Days 4 and 7), every subject chose 3.5% THC over 0.0% THC. During Blocks 3 and 4, on Days 8 through 13, subjects smoked about the same number of 2.0% and 3.5% cigarettes. On choice days, however, 3.5% THC was clearly preferred over 2.0% THC, in that 4 of 6 subjects chose the higher THC content on Day 10, and all 6 subjects chose 3.5% THC on Day 13.

The right panel of Figure 2 presents subjects' ratings of drug "liking." During the first two blocks, on Days 2 through 7, 3.5% THC ratings were higher than 0.0% THC ratings, with two exceptions (0.0% THC ratings were similar to or higher than 3.5% THC ratings on Days 2 and 3 for S4 and S5). Ratings were generally similar on sample and choice days. During Blocks 3 and 4, on Days 8 through 13, ratings of marijuana cigarettes containing 2.0% and 3.5% THC were generally similar. No consistent differences in ratings were observed on sampling and choice days.

GENERAL DISCUSSION

The results of these studies show clearly that the number of marijuana cigarettes smoked was not related to THC content. The number of cigarettes smoked per recreation period was generally similar across days, regardless of the THC content of the marijuana on any given day (see also Chait, 1989; Zacny & de Wit,

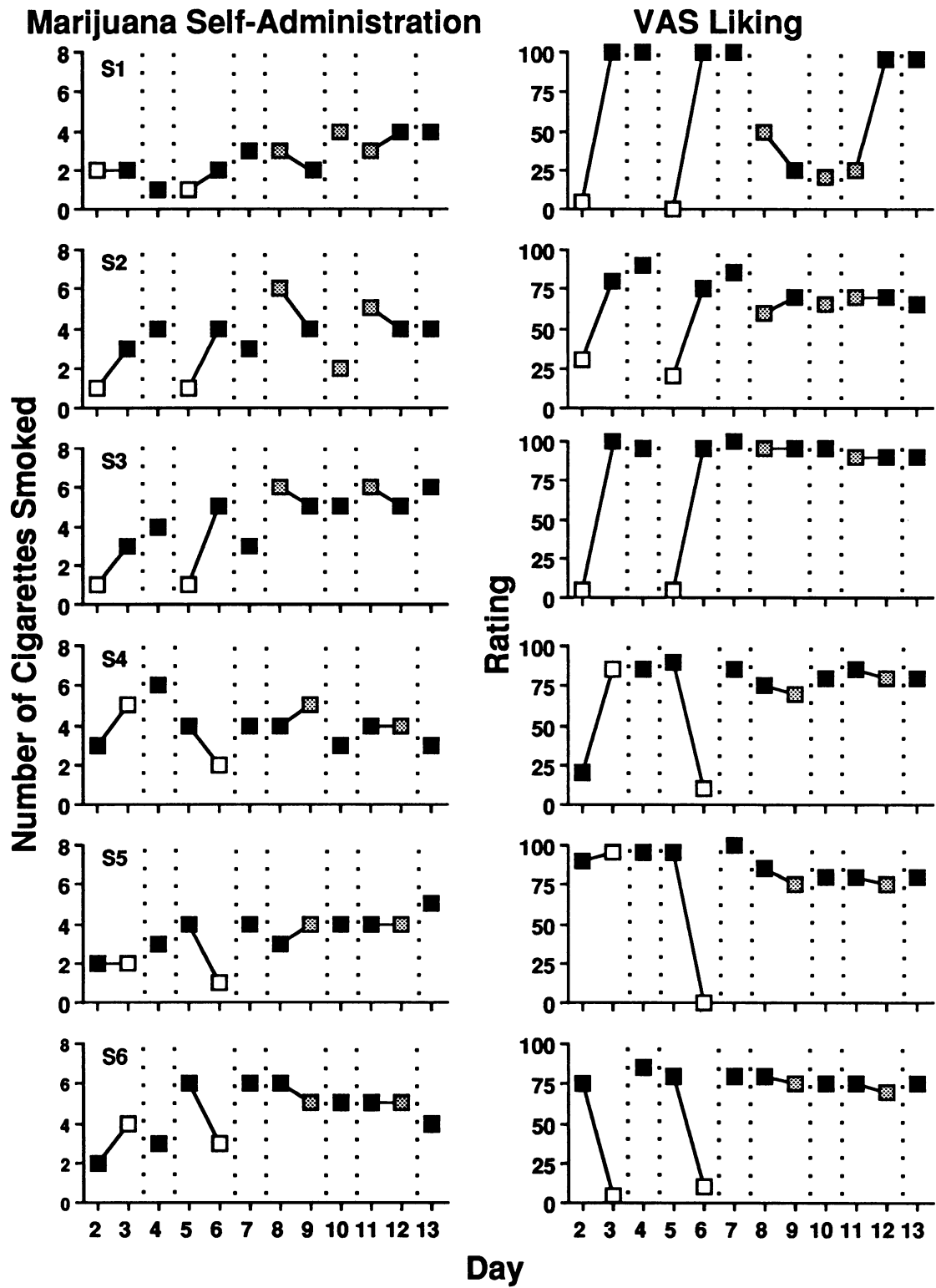


Fig. 2. Number of marijuana cigarettes smoked per day during the recreation period drug-availability interval (left column) and visual-analogue ratings of drug “liking” (right column) for each subject. Symbol backgrounds represent

1991). There was one experimental condition, however, under which subjects smoked more active marijuana cigarettes than placebo cigarettes. In the second experiment, during the second sampling occasion (i.e., Days 5 and 6), subjects consistently smoked more active marijuana cigarettes than placebo cigarettes. However, differences in the number of marijuana cigarettes smoked were not observed consistently when subjects first sampled placebo and active cigarettes (i.e., Days 2 and 3). It is possible that changes in marijuana cigarette smoking occurred as a result of providing subjects with a choice history—all subjects chose active marijuana cigarettes on the choice day (i.e., Day 4) separating these sampling occasions. However, additional studies will be required to rule out other possible factors, including differences in THC content between placebo and active marijuana cigarettes and changes in marijuana cigarette smoking over time.

Verbal report can be objectively defined and brought under experimental control (Perone, 1988). Using an objective visual-analogue scale, retrospective verbal reports of drug "liking" were obtained in these studies for comparison with marijuana self-administration. Subject reports of "liking" were higher following active marijuana than placebo, but were not related to the number of marijuana cigarettes that were smoked. However, although reports of "liking" varied between placebo and active marijuana cigarettes, there were minimal differences between the two active THC doses (i.e., 2.0% and 3.5%). Similarly, minimal differences were observed in the number of marijuana cigarettes containing 2.0% and 3.5% THC that were smoked. Similar patterns of differential reports of drug effects between placebo and active drug, but not between active doses, have been reported with other drugs as well (e.g., Fischman & Foltin, 1991).

In order to provide a more comprehensive assessment of the reinforcing effects of marijuana cigarettes, the second experiment included a choice condition. Subjects always chose to self-administer active marijuana cigarettes compared to placebo (12 of 12 occasions) and consistently chose to self-administer 3.5% THC compared to 2.0% THC (10 of 12 occasions),

confirming the results of previous studies of marijuana dose choice (Chait & Zacny, 1992; Mendelson & Mello, 1984). In contrast to reports of drug "liking" and the number of marijuana cigarettes smoked, dose choice was consistently sensitive to THC concentration and provided a clear demonstration of the influence of THC on the reinforcing effects of marijuana.

Measures of intake, choice, and drug "liking" have received extensive attention in the study of drug abuse liability (e.g., de Wit & Griffiths, 1991; Fischman, 1989; Foltin & Fischman, 1991; Preston & Jasinski, 1991; Vuchinich & Tucker, 1988). The administration of drugs of abuse produces a wide range of behavioral changes that can be measured under controlled conditions (e.g., ratings of drug "liking"). Although such effects are of critical importance for an understanding of the interactions between drugs and behavior, they do not always substitute effectively for direct measures of the reinforcing effects of drugs (e.g., Fischman & Foltin, 1991). In the current study, dose choice was the most sensitive measure of the influence of THC content on the reinforcing effects of marijuana. However, this result may have been influenced by experimental constraints. For example, the number of cigarettes smoked might have been related to THC content if dose conditions had been maintained for longer periods of time, or if there had been no constraints on smoking.

The unusually large discordance among outcome measures in these studies (i.e., drug intake, dose choice, and verbal report of drug "liking"; cf. Foltin & Fischman, 1992) suggests that additional research with marijuana may be useful to evaluate the relationship among measures of abuse liability. For example, isolating the factors that maintain the self-administration of placebo marijuana cigarettes, such as conditioned cues (e.g., the taste and feel of marijuana smoke passing through the mouth and throat, the increase in carbon monoxide levels), as has been reported for tobacco cigarette smoking (e.g., U.S. Department of Health and Human Services, 1988), might help to clarify the complex relationship among measures of abuse liability, as would a

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dose conditions (open symbols: 0% THC; gray symbols: 2.0% THC; solid symbols: 3.5% THC). Unconnected points represent separate sessions in which subjects chose between doses sampled in the preceding two sessions.

more comprehensive assessment of the stimulus effects of marijuana. Additional study of the influence of social context and drug-use history on marijuana self-administration will also be useful in examining this relationship.

The residential laboratory provided an ideal setting for an examination of marijuana self-administration. Safe and controlled drug self-administration was obtained in a contemporary living environment under controlled social conditions in which naturalistic patterns of behavior were uninterrupted while multiple behaviors were monitored over extended durations. Results indicated that dose choice was more sensitive to changes in THC content than either marijuana smoking or ratings of drug "liking." Drug ratings were sensitive to the presence and absence of THC, but not to differences in the amount of THC, and were not predictive of either the number of marijuana cigarettes smoked or of dose choice. The residential laboratory provides data, unobtainable in more traditional outpatient or inpatient settings, that are useful for comprehensive assessments of the abuse liability of marijuana and other drugs.

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